SUPPLEMENTAL MATERIAL

Thyroid Function Within the Normal Range, Subclinical Hypothyroidism and the Risk of Atrial Fibrillation

Supplemental Figure 5. Funnel Plot for the Association between Free Thyroxine within the Reference Range and Atrial Fibrillation

Supplemental Figure Legends

Supplemental References

Supplemental Methods 1. Data Sources and Search Strategies

We performed a systematic literature review on the risk of atrial fibrillation across the full TSH range in MEDLINE and EMBASE databases without language restriction from inception to July 27, 2016. We did our search on an Ovid (MEDLINE) server by using broadly defined Medical Subject Headings (MeSH): *thyroid diseases*, *hypothyroidism*, *hyperthyroidism*, *thyroid hormones*, *thyrotropin, atrial fibrillation, arrhythmia*; and the following keywords: *subclinical hypothyroidism*, *subclinical hyperthyroidism*, *subclinical dysthyroidism*, *subclinical thyroid,* and *euthyroid.* We used the filter designed by knowledge information specialists from BMJ to select prospective studies (MEDLINE cohort-study filter)[1] but without their year limitation. A search in EMBASE was done using similar terms. We also conducted a manual literature search with review of expert papers in the field and screened bibliographies from retrieved articles.

Supplemental Methods 2. Study Quality Assessment

Following individual criteria of the Newcastle-Ottawa Quality Assessment Scale[2] were assessed: 1-2) representativeness of the exposed/unexposed cohort (populations-based vs. convenience based), 3) ascertainment of exposure (thyroid function measurement), 4) demonstration that outcome of interest (atrial fibrillation) was not present at start of study, 5) availability of relevant confounders for adjustment, 6) objective assessment of outcome (assessment of atrial fibrillation by electrocardiogram), 7) adequate length of follow-up period (>5 years), and 8) loss of follow-up (<5%). Two authors independently assessed study quality (C.B. and C.F.).

Supplemental Table 1. Definition of Baseline Covariates

Study	Smoking	Diabetes	Prevalent Cardiovascular Disease
Cardiovascular Health Study[4]	Self-reported never, former, or current smoking (≥100 cigarettes in entire life)	Fasting glucose level of ≥126mg/dL or use of hypoglycemic medication	History of myocardial infarction or angina or CABG or angioplasty or stroke or TIA (adjudicated)
Health ABC Study[9]	Self-reported never, former, or current smoking (≥100 cigarettes in entire life)	Self-reported diagnosis of diabetes or use of hypoglycemic medication	Self-reported history of myocardial infarction or angina with use of antianginal medications or CABG or angioplasty or stroke or TIA
Osteoporotic Fractures in Men (MrOS) Study[10]	Self-reported never, former, or current smoking	Self-reported diagnosis of diabetes	Self-reported myocardial infarction or stroke
Bari Study[11]	Self-reported non-smoker or current smoker (regular smoking within last 30 days)	Physician diagnosis of diabetes	History of myocardial infarction or angina or CABG or angioplasty or stroke (assessed by review of medical records)
Leiden 85-plus Study[12]	Self-reported never, former, or current smoking	Physician diagnosis of diabetes or use of hypoglycemic medication	History of myocardial infarction or angina or stroke (assessed by review of medical records, physician or self-report, and ECG)
SHIP[13]	Self-reported never, former, or current smoking	Self-reported or physician diagnosis of diabetes	Self-reported myocardial infarction or CABG or stroke
InChianti Study[14]	Self-reported never, former, or current smoking (if at least 1 year of cigarette smoking)	Fasting blood glucose >140 mg/dL or glucosuria	History of myocardial infarction or angina or perfusion deficit/asynergy in scintigraphy or severe stenosis in coronary angiography or CABG or angioplasty or stroke (adjudicated)
Rotterdam Study[8]	Self-reported never, former, or current smoking	Random or post-load serum glucose level of 200mg/dL or higher, or use of hypoglycemic medication	History of myocardial infarction or revascularization or stroke (assessed by self-report, ECG, review of nationwide Medical Registry, screening of physician records)
PROSPER Study[15]	Self-reported never, current, or former smoking	Self-reported diagnosis of diabetes or use of hypoglycemic drugs or fasting blood glucose of 7.0mmol/l or 11.1mmol/l or greater when fasting status was uncertain	Physician diagnosis of vascular disease or myocardial infarction or angina or CABG or angioplasty or stroke or TIA
EPIC-Norfolk Study[16]	Self-reported never, former, or current smoking (if ≥1 cigarette a day for ≥1 year)	Self-reported diagnosis of diabetes	Self-reported myocardial infarction or stroke
Busselton Health Study[17]	Self-reported never, former, or current smoking	Self-reported diagnosis of diabetes, use of hypoglycemic drugs, or glucose level >200 mg/dL 2 hours after glucose load	History of myocardial infarction or angina (assessed by self-reported confirmation of physician diagnosis, Rose questionnaire, ECG)

Abbreviations: CABG, coronary artery bypass surgery; ECG, electrocardiogram; TIA, transient ischemic attack

Supplemental Table 2. Studies Excluded after Full Text Screening

Reason for exclusion	References
Review, meeting abstract, poster or editorial	Erichsen R, Christiansen CF, Froslev T, Jacobsen J, Sorensen HT. Intravenous bisphosphonate therapy and risk of atrial fibrillation in cancer patients. *Pharmacoepidemiology and Drug Safety.* 2011;20((Erichsen R.; Christiansen C.F.; Froslev T.; Jacobsen J.; Sorensen H.T.) Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark):S121. Kim SC, Liu J, Solomon DH. The risk of atrial fibrillation in patients with rheumatoid arthritis compared to the general population: A large cohort study. *Arthritis and Rheumatism.* 2012;64((Kim S.C.) Brigham and Women's Hospital, Boston, United States):S722. Nanchen D, Gussekloo J, Westendorp RGJ, et al. Subclinical thyroid dysfunction and the risk of heart failure, other cardiovascular events and mortality in the elderly. *Journal of General Internal Medicine.* 2011;26((Nanchen D.; Gussekloo J.; Westendorp R.G.J.; Jukema J.W.; Trompet S.; Mooijaart S.P.; De Craen A.J.M.) Leiden University Medical Center, Leiden, Netherlands):S140. Stojanovic M, Sabljak V, Markovic D, Ladjevic N, Zivaljevic V, Kalezic N. New onset atrial fibrillation during goitre surgery. *European Journal of Anaesthesiology.* 2013;30((Stojanovic M.; Sabljak V.; Markovic D.; Ladjevic N.; Zivaljevic V.; Kalezic N.) Clinical Centre of Serbia, Dept of Anaesthesiology, Belgrade, Serbia):28. Chelazzi C, Giugni D, Villa G, De Gaudio R. Postoperative atrial fibrillation among non cardio-thoracic surgical patients: Associated clinical factors and outcome. *Critical Care Medicine.* 2011;39((Chelazzi C.; Giugni D.; Villa G.; De Gaudio R.) University of Florence, Italy):148. Rothstein M, Pereira E, Baker S, Arora R, Bhatkar V, Colombo J. Parasympathetic involvement in sleep medicine, cardiovascular implications. *Clinical Autonomic Research.* 2011;21(4):298. Ryodi E, Salmi J, Valimaki M, et al. Cardiovascular morbidity after surgical treatment of hyperthyroidism - A nationwide cohort study with a long-term follow-up. *Endocrine Reviews.* 2012;33(3). Selmer C, Olesen J, Lindhardsen J, et al. Subclinical thyroid disease and risk of new-onset atrial fibrillation. *Journal of the American College of Cardiology.* 2012;59(13):E662. Proenca M, Cardiga R, Araujo I, et al. Prognostic value of subclinical hyperthyroidism in an internal medicine ward. *European Journal of Internal Medicine.* 2013;24((Proenca M.; Cardiga R.; Araujo I.; Marques F.; Jesus S.; Cardoso D.; Serra S.; Fonseca C.; Leitao A.; Ceia F.) Medicine III, Sao Francisco Xavier Hospital, Lisbon, Portugal):e102. Mueller PS. Thyroid function and risk for AF: A linear relation. *Medicine Today.* 2013;14(1):64.
No prospective cohort study	Collet T-H, Gussekloo J, Bauer DC, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Archives of Internal Medicine.* 2012;172(10):799-809. Katircibasi MT, Deniz F, Pamukcu B, Binici S, Atar I. Effects of short-term propylthiouracil treatment on p wave duration and p wave dispersion in patients with overt hypertyroidism. *Experimental & Clinical Endocrinology & Diabetes.* 2007;115(6):376-379. Tanase DM, Ionescu SD, Ouatu A, Ambarus V, Arsenescu-Georgescu C. Risk assessment in the development of atrial fibrillation at patients with associate thyroid dysfunctions. *Revista Medico-Chirurgicala a Societatii de Medici Si Naturalisti Din Iasi.*

	2013;117(3):623-629. Tenerz A, Forberg R, Jansson R. Is a more active attitude warranted in patients with subclinical thyrotoxicosis? *Journal of Internal Medicine.* 1990;228(3):229-233. Selmer C, Olesen JB, Hansen ML, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *BMJ.* 2012;345:e7895. Ruigomez A, Johansson S, Wallander M-A, Garcia Rodriguez LA. Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. *BMC Cardiovascular Disorders.* 2005;5:20. Aras D, Maden O, Ozdemir O, et al. Simple electrocardiographic markers for the prediction of paroxysmal atrial fibrillation in hyperthyroidism. *International Journal of Cardiology.* 2005;99(1):59-64. Klein Hesselink EN, Lefrandt JD, Schuurmans EP, et al. Increased Risk of Atrial Fibrillation After Treatment for Differentiated Thyroid Carcinoma. *The Journal of clinical endocrinology and metabolism.* 2015; 100(12):4563-9
No measurement of both serum thyroid stimulating hormone and thyroxine at baseline	Geng J, Hu T, Wang B, Lu W, Ma S. Thyroid stimulating hormone levels and risk of coronary heart disease in patients with type 2 diabetes mellitus. *International Journal of Cardiology.* 2014;174(3):851-853. Kim E-J, Lyass A, Wang N, et al. Relation of hypothyroidism and incident atrial fibrillation (from the Framingham Heart Study). *American Heart Journal.* 2014;167(1):123-126.
No explicit assessment of atrial fibrillation outcome events	Trivalle C, Doucet J, Chassagne P, et al. Differences in the signs and symptoms of hyperthyroidism in older and younger patients. *Journal of the American Geriatrics Society.* 1996;44(1):50-53. Kentsch M, Otter W, Kroger B, et al. [Bradycardia despite hyperthyroidism]. *Zeitschrift fur Kardiologie.* 2001;90(7):492-497. Nasim A, Shahzad A, Saeed S. Medium term effectiveness of thyroxine treatment in congestive cardiac failure (CCF). *Journal of Postgraduate Medical Institute.* 2009;23(2):124-134. Yonem O, Dokmetas HS, Aslan SM, Erselcan T. Is antithyroid treatment really relevant for young patients with subclinical hyperthyroidism? *Endocrine Journal.* 2002;49(3):307-314. Azemi T, Bhavnani S, Kazi F, et al. Prognostic impact of thyroid stimulating hormone levels in patients with cardiomyopathy. *Connecticut Medicine.* 2013;77(7):409-415. Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. *American Heart Journal.* 2001;142(5):838-842. Akdemir R, Ebru Eryasar N, Celik K, et al. Increased P wave dispersion in hypothyroidism: A sign of risk of atrial fibrillation. *Turkish Journal of Medical Sciences.* 2009;39(4):629-633. Osman F, Franklyn JA, Daykin J, et al. Heart rate variability and turbulence in hyperthyroidism before, during, and after treatment. *American Journal of Cardiology.* 2004;94(4):465-469. Ceresini G, Marina M, Lauretani F, et al. Relationship Between Circulating Thyroid-Stimulating Hormone, Free Thyroxine, and Free Triiodothyronine Concentrations and 9-Year Mortality in Euthyroid Elderly Adults. *Journal of the American Geriatrics Society.* 2016;64(3):553-60.
Studies assessing only postoperative atrial fibrillation events	Cerillo AG, Bevilacqua S, Storti S, et al. Free triiodothyronine: a novel predictor of postoperative atrial fibrillation. *European Journal of Cardio-Thoracic Surgery.* 2003;24(4):487-492. Kokkonen L, Majahalme S, Koobi T, et al. Atrial fibrillation in elderly patients after cardiac surgery: postoperative hemodynamics

and low postoperative serum triiodothyronine. *Journal of Cardiothoracic & Vascular Anesthesia.* 2005;19(2):182-187.
Park YJ, Yoon JW, Kim KI, et al. Subclinical hypothyroidism might increase the risk of transient atrial fibrillation after coronary artery bypass grafting. *Annals of Thoracic Surgery.* 2009;87(6):1846-1852.
Guden M, Akpinar B, Saggbas E, Sanisoglu I, Cakali E, Bayindir O. Effects of intravenous triiodothyronine during coronary artery bypass surgery. *Asian Cardiovascular & Thoracic Annals.* 2002;10(3):219-222.
Ozcan S. Relationship between atrial fibrilation and coronary bypass surgery. *Pakistan Journal of Medical Sciences.* 2014;30(3):630-633.

Supplemental Table 3. Baseline Characteristics of Participants by Thyroid Function

Characteristic	Euthyroidism (n=28,127)	Subclinical Hypothyroidism (n=1,958)	p-value*
Age in y, mean (SD)	64.4 (13.5)	69.9 (10.0)	<0.001
Women, n (%)	14,285 (50.8)	1,223 (62.5)	<0.001
Caucasian, n (%) †	18,095 (91.8)	1,406 (91.8)	0.92
Body mass index in kg/m^2, mean (SD) ‡	26.6 (4.2)	26.8 (4.3)	0.072
Thyroid stimulating hormone in mIU/L, mean (SD)	1.81 (0.91)	6.68 (2.59)	<0.001
Present or former smoker, n (%)	15,799 (56.2)	980 (50.1)	<0.001
Systolic blood pressure in mmHg, mean (SD) §	139.2 (21.5)	139.6 (22.4)	0.36
Total cholesterol in mmol/l, mean (SD) ||	6.08 (1.67)	5.94 (1.38)	<0.001
Cardiovascular disease, n (%)	4,928 (17.5)	443 (22.6)	<0.001
Heart failure, n (%)	655 (2.3)	59 (3.0)	0.054
Stroke, n (%)	624 (2.2)	61 (3.1)	0.010
Diabetes, n (%)	2,108 (7.5)	196 (10.0)	<0.001
Antihypertensive medication, n (%)	10,593 (37.7)	878 (44.8)	<0.001
Lipid-lowering medication, n (%)	3,772 (13.4)	305 (15.6)	0.007
Amiodarone, n (%) #	101 (0.4)	22 (1.1)	<0.001

Abbreviation: SD, standard deviation.

*p-values were derived from a chi-squared test or Student's t-test, as appropriate

† Information on race was missing in 8,408 (29.9%) participants with euthyroidism and 427 (21.8%) with subclinical hypothyroidism

‡ Information on body mass index was missing in 128 (0.5%) participants with euthyroidism and 11 (0.6%) with subclinical hypothyroidism

§ Information on systolic blood pressure was missing in 79 participants with euthyroidism (0.3%) and 4 (0.2%) with subclinical hypothyroidism

|| Information on total cholesterol was missing in 126 (0.4%) participants with euthyroidism and 7 (0.4%) with subclinical hypothyroidism

Information on amiodarone use at baseline was missing in all participants of the Busselton Health Study (1,023 participants with euthyroidism and 37 with subclinical hypothyroidism)

Supplemental Table 4. Quality Assessment of Included Studies*

Study	Population studied †	Ascertainment of exposure ‡	Assessment of AF at baseline	Controlling for additional factors	Methods for AF ascertainment	Duration of follow-up, median (IQR), y	Lost to follow-up (%)
United States							
Cardiovascular Health Study	P, 4 communities (USA)	Third generation TSH assay	yes	age and sex, systolic blood pressure, current or former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease, lipid lowering medications, antihypertensive medications, BMI, heart rate, and alcohol consumption	Self-report, annual ECG, ICD-9 hospital discharge codes	11.7 (7.0-18.1)	7.9-10.1
Health ABC Study	P, 2 cities (USA)	Third generation TSH assay	yes	age and sex, systolic blood pressure, current or former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease, lipid lowering medications, antihypertensive medications, BMI, heart rate, and alcohol consumption	Recoded Minnesota at baseline and year 4 follow-up visits, ICD-9 coded diagnoses from CMS (center for Medicare and Medicaid) data	8.1 (7.4-8.3)	<5
Osteoporotic Fractures in Men (MrOS) Study	P, 6 clinical centers (USA)	Third generation TSH assay	yes	age and sex, systolic blood pressure, current or former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease, lipid lowering medications, antihypertensive medications, BMI, heart rate, and alcohol consumption	self report and ECG at baseline, medical records and supporting documentation collected every 4months (phone or postcard follow-up)	12.6 (11.2-13.1)	6
Europe							
Bari Study	Outpatients with congestive heart failure (Italy)	Third generation TSH assay	yes	age and sex, systolic blood pressure, current or former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease, lipid lowering medications, antihypertensive medications, BMI	ICD-9 at discharge	1.3 (0.6-1.9)	<5

Leiden 85+ Study	P, 1 town (Leiden, The Netherlands)	Third generation TSH assay	yes	age and sex, systolic blood pressure, current or former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease, lipid lowering medications, antihypertensive medications, BMI, and alcohol consumption	Annual ECG, Minnesota	5.5 (2.7-9.0)	<5
Study of Health in Pomerania	P, 1 region (West Pomerania, Germany)	Third generation TSH assay	yes	age and sex, systolic blood pressure, current or former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease, lipid lowering medications, antihypertensive medications, BMI, heart rate	Minnesota at baseline + year 5 follow-up and ongoing year 10 follow-up	11.5 (11.1-12.1)	37
Invecchiare in Chianti Study	P, 2 towns in Toscany (Italy)	Third generation TSH assay	yes	age and sex, systolic blood pressure, current or former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease, lipid lowering medications, antihypertensive medications, BMI, heart rate, and alcohol consumption	ECG at baseline and year 3 follow-up, year 6 follow-up and year 9 follow-up	9.0 (8.3-9.2)	35
Rotterdam Study	P, 1 district (The Netherlands)	Third generation TSH assay	yes	age and sex, systolic blood pressure, current or former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease, lipid lowering medications, antihypertensive medications, BMI, heart rate, and alcohol consumption	i) 12 lead ECG at baseline and follow-up visits ii) ICD-10 coded info from GPs (own records, hospital discharge letters) with requirement of ECG verifying the diagnosis iii) hospital discharge diagnoses through Dutch National Medical Registration	15.5 (11.4-16.9)	0.9
PROSPER Study	Primary care patients, in 3 countries (The Netherlands, Ireland, Scotland)	Third generation TSH assay	yes	age and sex, systolic blood pressure, current or former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease, lipid lowering medications, antihypertensive medications, BMI, heart rate, and alcohol consumption	Annual single-lead ECG or 12-lead ECG or telemetry during hospitalization or other clinical care	3.3 (3.0-3.5)	<5

EPIC-Norfolk	P, 1 county (Norfolk, England)	Third generation TSH assay	yes	age and sex, systolic blood pressure, current or former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease, lipid lowering medications, antihypertensive medications, BMI, heart rate, and alcohol consumption	Baseline: self-reported intake of drugs used for AF treatment: digitalis and vitamin K antagonists. Incident AF: ICD-10 coded hospital discharge codes	17.0 (16.1-18.0)	<2
Australia							
Busselton Health Study	P, 1 district (Busselton, Australia)	Third generation TSH assay	yes	age and sex, systolic blood pressure, current or former smoking, diabetes mellitus, total cholesterol, and prevalent cardiovascular disease, antihypertensive medications, BMI	ECG at baseline and year 14 follow-up	14.0 (14.0-14.0)	37

Abbreviations: AF, atrial fibrillation; BMI, body mass index; ECG, electrocardiogram; GP, general practitioner; NR, not reported; P, population-based study.

*If an article did not clearly mention one of these characteristics, we considered that is had not been done. All included studies were prospective cohort studies.

† A population-based study was defined as a random sample of the general population.

‡ A formal adjudication procedure was defined as having clear criteria for the outcome that were reviewed by experts for each potential case.

Supplemental Table 5. Sensitivity Analyses of the Association between Thyroid Stimulating Hormone within the Reference Range and the Risk of Atrial Fibrillation

TSH level (mIU/l)	0.45-0.99		1.00-1.49		1.50-2.49		2.50-3.49		3.50-4.49	
	Events / Persons	HR (95% CI)	Events / Persons	HR (95% CI)	Events / Persons	HR (95% CI)	Events / Persons	HR (95% CI)	Events / Persons	HR (95% CI)
Main analysis (age- and sex-adjusted)	372/5665	1.10 (0.92-1.31)	492/6275	1.03 (0.87-1.22)	893/9990	1.04 (0.89-1.22)	412/4391	0.94 (0.79-1.12)	190/1806	ref.
Excluding users of amiodarone and a study with missing relevant data*	365/5369	1.09 (0.91-1.30)	485/5956	1.02 (0.86-1.21)	883/9622	1.03 (0.88-1.21)	408/4293	0.93 (0.78-1.11)	190/1763	ref.
Excluding thyroid medication use at BL and/or FUP and studies with missing relevant data †	225/3510	1.05 (0.84-1.32)	306/3286	1.01 (0.82-1.25)	596/4994	1.06 (0.88-1.29)	292/2412	0.96 (0.78-1.18)	124/945	ref.

Abbreviations: BL, baseline; CI, confidence interval; FUP, follow-up; HR, hazard ratio; TSH, thyroid stimulating hormone.

* A total of 1,183 participants were excluded for this sensitivity analysis of the association between TSH and atrial fibrillation: 2 participants who took amiodarone in the Cardiovascular Health Study; 3 in the Health ABC Study; 1 in the Osteoporotic Fractures in Men Study; 79 in the Bari Study; 1 in the Leiden 85+ Study; 1 in the Study of Health in Pomerania; 6 in the Invecchiare in Chianti Study; 6 in the Rotterdam Study; 23 in the PROSPER Study; 1 in the EPIC-Norfolk Study, and all 1,060 participants from the Busselton Health Study, in which information on amiodarone use was not available.

† The number of thyroid medication users during follow-up are indicated in Table 1. We additionally excluded 11,642 participants in the EPIC-Norfolk Study and 1,607 in the Rotterdam Study from this sensitivity analysis on the association between TSH and atrial fibrillation, because information on thyroid medication use during follow-up was not available in these studies.

Supplemental Table 6. Stratified Analyses for the Association between Thyroid Stimulating Hormone within the Reference Range and Atrial Fibrillation*

TSH level (mIU/l)	0.45-0.99			1.00-1.49			1.50-2.49			2.50-3.49			3.50-4.49
Variable	Events/ Persons	HR (95% CI)	HR (95%CI)	Events/ Persons	HR (95% CI)	HR (95% CI)	Events/ Persons	HR (95% CI)	HR (95% CI)	Events/ Persons	HR (95% CI)	HR (95% CI)	Events/ Persons
		Age/Sex Adj	Multivariate Model §		Age/Sex Adj	Multivariate Model ‡		Age/Sex Adj	Multivariate Model ‡		Age/Sex Adj	Multivariate Model ‡	
Total Population	372/5665	1.10 (0.92-1.31)	1.07 (0.89-1.28)	492/6275	1.03 (0.87-1.22)	0.99 (0.84-1.18)	893/9990	1.04 (0.89-1.22)	1.02 (0.87-1.19)	412/4391	0.94 (0.79-1.12)	0.92 (0.78-1.10)	190/1806
Age, y													
18-64	59/3051	0.82 (0.48-1.42)	0.86 (0.50-1.47)	67/2760	0.83 (0.49-1.41)	0.87 (0.51-1.47)	102/3935	0.81 (0.49-1.33)	0.78 (0.47-1.30)	34/1367	0.81 (0.46-1.44)	0.78 (0.44-1.37)	18/563
≥65	313/2614	1.06 (0.88-1.28)	1.04 (0.86-1.25)	425/3515	0.97 (0.82-1.16)	0.94 (0.79-1.13)	791/6055	1.03 (0.87-1.21)	1.01 (0.85-1.19)	378/3024	0.92 (0.77-1.11)	0.91 (0.76-1.09)	172/1243
P for Trend		0.97	0.97		0.97	0.97		0.97	0.97		0.97	0.97	
Sex													
Women	160/2791	1.03 (0.80-1.32)	1.00 (0.78 -1.28)	210/3079	0.97 (0.76-1.22)	0.93 (0.74-1.18)	408/4967	1.02 (0.82-1.26)	1.00 (0.80- 1.24)	202/2352	0.93 (0.74-1.18)	0.91 (0.72-1.16)	107/1096
Men	212/2874	1.16 (0.89-1.50)	1.13 (0.87-1.47)	282/3196	1.11 (0.87-1.42)	1.07 (0.83-1.37)	485/5023	1.09 (0.86 to 1.38)	1.06 (0.84-1.35)	210/2039	0.97 (0.75-1.25)	0.95 (0.73-1.23)	83/710
P for Interaction		0.64	0.81		0.64	0.81		0.64	0.81		0.64	0.81	
Race †													
White	247/2763	1.19 (0.97-1.46)	1.17 (0.95-1.44)	332/4059	1.00 (0.83-1.22)	0.96 (0.79-1.17)	619/6922	1.01 (0.84-1.20)	0.97 (0.81-1.17)	292/3038	0.90 (0.74-1.09)	0.87 (0.72-1.06)	153/1313
Non-white	23/268	0.95 (0.42-2.12)	0.92 (0.41-2.07)	47/381	1.48 (0.70-3.13)	1.38 (0.65-2.93)	68/610	1.40 (0.67-2.91)	1.34 (0.64-2.80)	35/264	1.63 (0.75-3.51)	1.51 (0.70-3.27)	8/101
P for Interaction		0.037	0.033		0.037	0.033		0.037	0.033		0.037	0.033	
Previous CVD													
None ‡	263/4876	1.15 (0.93-1.42)	1.14 (0.92-1.41)	349/5196	1.10 (0.90-1.34)	1.08 (0.88-1.32)	616/8186	1.07 (0.89-1.29)	1.05 (0.87-1.28)	278/3471	0.96 (0.78-1.18)	0.96 (0.78-1.19)	132/1470
Yes	109/789	0.91 (0.66-1.26)	0.91 (0.66-1.26)	143/1079	0.82 (0.61-1.12)	0.81 (0.60-1.10)	277/1804	0.92 (0.70-1.23)	0.93 (0.70-1.24)	134/920	0.84 (0.62-1.14)	0.83 (0.60-1.13)	58/336
P for Interaction		0.78	0.74		0.78	0.74		0.78	0.74		0.78	0.74	
Thyroxine use at BL													
None	372/5665	1.10 (0.92-1.31)	1.07 (0.89-1.28)	492/6275	1.03 (0.87-1.22)	0.99 (0.84-1.18)	893/9990	1.04 (0.89-1.22)	1.02 (0.87-1.19)	412/4391	0.94 (0.79-1.12)	0.92 (0.78-1.10)	190/1806
Yes	27/244	1.28 (0.62-2.66)	1.45 (0.68-3.10)	22/154	1.57 (0.74-3.33)	1.65 (0.76-3.60)	32/233	1.52 (0.74-3.10)	1.60 (0.76-3.37)	19/139	1.42 (0.66-3.07)	1.52 (0.68-3.39)	10/105
P for Interaction		0.37	0.31		0.37	0.31		0.37	0.31		0.37	0.31	

Abbreviations: Adj, adjusted; AF, atrial fibrillation; BL, baseline; CI, confidence interval; CVD, cardiovascular disease; E, events; HR, hazard ratio; NA, data not applicable; P, participants; TSH, thyroid-stimulating hormone

* The TSH category 3.50-4.49mIU/l was the reference category

† African Americans, Hispanics, Asian, and others were considered as non-white population. Data on race were missing for all participants of the SHIP study, the InChianti Study, and the PROSPER Study, 67 participants of the Rotterdam Study and 44 of the EPIC-Norfolk Study.

‡ Previous cardiovascular was defined as a history of stroke, transient ischemic attack, myocardial infarction, angina pectoris, coronary angioplasty, bypass surgery. Participants without any of these events were considered having no previous cardiovascular disease.

§ Adjusted for age, sex, systolic blood pressure, current and former smoking, diabetes, total cholesterol and prevalent cardiovascular disease.

Supplemental Table 7. Sensitivity Analyses of the Association between Subclinical Hypothyroidism and the Risk of Atrial Fibrillation

TSH level (mIU/l)	3.50-4.49		4.5-6.9		7.0-9.9		10.0-19.9	
	Events / Participants	HR (95% CI)	Events / Participants	HR (95% CI)	Events / Participants	HR (95% CI)	Events / Participants	HR (95% CI)
Main analysis (age- and sex-adjusted)	190/1806	ref.	149/1384	0.92 (0.74-1.14)	44/383	1.02 (0.73-1.41)	22/191	0.94 (0.61-1.47)
Excluding users of amiodarone and a study with missing relevant data*	190/1763	ref.	146/1355	0.90 (0.73-1.12)	43/371	1.00 (0.72-1.39)	20/173	0.90 (0.57-1.42)
Excluding thyroid medication use at BL and/or FUP and studies with missing relevant data †	124/945	ref.	81/719	0.87 (0.66-1.16)	22/147	1.22 (0.78-1.92)	11/60	1.56 (0.84-2.90)

Abbreviations: BL, baseline; CI, confidence interval; FUP, follow-up; HR, hazard ratio; TSH, thyroid stimulating hormone.

* Information on amiodarone use at baseline was not available in the Busselton Health Study.

† The number of thyroid medication users during follow-up are indicated in Table 1. We additionally excluded participants in the EPIC-Norfolk Study and the Rotterdam Study, because information on thyroid medication use during follow-up was not available in these studies.

Supplemental Table 8. Stratified Analyses for the Association between Subclinical Hypothyroidism and Atrial Fibrillation*

TSH level (mIU/l)	3.50-4.49	4.5-6.9			7.0-9.9			10.0-19.9		
Variable	**Events/ Persons**	**Events/ Persons**	**HR (95% CI)**	**HR (95%CI)**	**Events/ Persons**	**HR (95% CI)**	**HR (95% CI)**	**Events/ Persons**	**HR (95% CI)**	**HR (95% CI)**
			Age/Sex Adj	**Multivariate Model §**		**Age/Sex Adj**	**Multivariate Model ‡**		**Age/Sex Adj**	**Multivariate Model ‡**
Total Population	190/1806	149/1384	0.92 (0.74-1.14)	0.91 (0.74-1.14)	44/383	1.02 (0.73-1.41)	0.95 (0.68-1.33)	22/191	0.94 (0.61-1.47)	0.93 (0.60-1.44)
Age										
18-64	18/563	7/339	0.69 (0.29-1.64)	0.67 (0.28-1.60)	2/91	0.72 (0.17-3.09)	0.79 (0.18-3.40)	1/51	0.66 (0.09-4.95)	0.76 (0.10-5.70)
≥65	172/1243	142/1045	0.95 (0.76-1.19)	0.96 (0.76-1.19)	42/292	1.02 (0.72-1.42)	0.96 (0.68-1.34)	21/140	1.05 (0.67-1.65)	1.03 (0.65-1.62)
P for Trend			0.97	0.97		0.97	0.97		0.97	0.97
Sex										
Women	107/1096	75/853	0.79 (0.59-1.06)	0.80 (0.60-1.08)	25/249	0.96 (0.62-1.48)	0.90 (0.58-1.40)	10/121	0.71 (0.37-1.37)	0.73 (0.38-1.39)
Men	83/710	74/531	1.11 (0.81-1.52)	1.07 (0.78-1.47)	19/134	1.10 (0.67-1.81)	1.01 (0.60-1.68)	12/70	1.27 (0.69-2.34)	1.21 (0.66-2.22)
P for Interaction			0.64	0.81		0.64	0.81		0.64	0.81
Race †										
White	153/1313	133/989	1.03 (0.82-1.30)	1.01 (0.80-1.28)	39/278	1.14 (0.80-1.62)	1.05 (0.73-1.50)	18/139	0.94 (0.58-1.54)	0.93 (0.57-1.52)
Non-white	8/101	5/90	0.58 (0.19-1.78)	0.54 (0.17-1.64)	1/25	0.41 (0.05-3.25)	0.38 (0.05-3.07)	0/10	NA	NA
P for Interaction			0.037	0.033		0.037	0.033		0.037	0.033
Previous CVD										
None ‡	132/1470	100/1078	0.97 (0.75-1.26)	0.99 (0.76-1.29)	28/291	0.98 (0.65-1.48)	0.93 (0.61-1.41)	16/146	1.11 (0.66-1.87)	1.13 (0.67-1.90)
Yes	58/336	49/306	0.76 (0.52-1.11)	0.77 (0.53-1.14)	16/92	1.00 (0.58-1.74)	0.99 (0.57-1.73)	6/45	0.65 (0.28-1.52)	0.67 (0.29-1.55)
P for Interaction			0.78	0.74		0.78	0.74		0.78	0.74
Thyroxine use at BL										
None	190/1806	149/1384	0.92 (0.74-1.14)	0.91 (0.74-1.14)	44/383	1.02 (0.73-1.41)	0.95 (0.68-1.33)	22/191	0.94 (0.61-1.47)	0.93 (0.60-1.45)
Yes	10/105	13/135	0.98 (0.43-2.24)	0.95 (0.40-2.26)	3/73	0.45 (0.12-1.63)	0.53 (0.14-1.95)	11/63	1.87 (0.79-4.41)	1.95 (0.81-4.74)
P for Interaction			0.37	0.31		0.37	0.31		0.37	0.31

Abbreviations: AF, atrial fibrillation; BL, baseline; CI, confidence interval; CVD, cardiovascular disease; E, events; HR, hazard ratio;

NA, data not applicable; P, participants; TSH, thyroid-stimulating hormone

* The TSH category 3.50-4.49mIU/l was the reference category

† African Americans, Hispanics, Asian, and others were considered as non-white population. Data on race were missing for all participants of the SHIP study, the InChianti Study, and the PROSPER Study, 67 participants of the Rotterdam Study and 44 of the EPIC-Norfolk Study.

‡ Previous cardiovascular was defined as a history of stroke, transient ischemic attack, myocardial infarction, angina pectoris, coronary angioplasty, bypass surgery. Participants without any of these events were considered having no previous cardiovascular disease.

§ Adjusted for age, sex, systolic blood pressure, current and former smoking, diabetes, total cholesterol and prevalent cardiovascular disease.

Supplemental Table 9. Sensitivity Analyses of the Association between Quartiles of Free Thyroxine within the Reference Range and the Risk of Atrial Fibrillation

fT4 quartile	First quartile		Second quartile		Third quartile		Fourth quartile		
	Events / Participants	HR (95% CI)	Events / Participants	HR (95% CI)	Events / Participants	HR (95% CI)	Events / Participants	HR (95% CI)	P for trend
Main analysis (age- and sex-adjusted)	371/5642	ref.	390/4989	1.17 (1.02-1.35)	438/5272	1.25 (1.09-1.43)	474/5018	1.45 (1.26-1.66)	≤0.001
Excluding users of amiodarone and a study with missing relevant data *	367/5245	ref.	389/4817	1.17 (1.02-1.35)	433/5000	1.24 (1.08-1.42)	463/4793	1.42 (1.24-1.63)	≤0.001
Excluding thyroid medication use at BL and/or FUP and studies with missing relevant data †	211/2345	Ref.	238/2063	1.17 (0.97-1.40)	218/2115	1.16 (0.96-1.40)	250/2063	1.37 (1.14-1.64)	0.002

Abbreviations: BL, baseline; CI, confidence interval; fT4; free thyroxine; FUP, follow-up; HR, hazard ratio.

* A total of 1,066 participants were excluded for this sensitivity analysis of the association between fT4 and atrial fibrillation: 1 participant who took amiodarone in the CHS; 1 in the MrOS; 57 in the Bari Study; 3 in the InChianti Study; 1 in the EPIC-Norfolk Study, and all 1003 participants in the Busselton Health Study, in which information on amiodarone use was not available.

† A total of 12,335 participants were excluded for this sensitivity analysis of the association between fT4 and atrial fibrillation: 139 participants in the CHS; 11 in the MrOS; 15 in the Bari Study; 3 in the Leiden 85+ Study; 156 in the SHIP; 13 in the InChianti Study; 2 in the PROSPER Study; and 9 in the Busselton Health Study; and all 10,745 participants in the EPIC-Norfolk Study and all 1,242 participants in the Rotterdam Study, because information on thyroid medication use during follow-up was not available in these studies.

Supplemental Table 10. Stratified Analyses for the Association between Quartiles of Free Thyroxine within the Reference Range and the Risk of Atrial Fibrillation *

fT4 Quantile	First Quartile			Second Quartile			Third Quartile			Fourth Quartile		
Variable	Events/ Persons	HR (95% CI)	HR (95%CI)	Events/ Persons	HR (95% CI)	HR (95% CI)	Events/ Persons	HR (95% CI)	HR (95% CI)	Events/ Persons	HR (95% CI)	HR (95% CI)
		Age/Sex Adj	Multivariate Model §		Age/Sex Adj	Multivariate Model §		Age/Sex Adj	Multivariate Model §		Age/Sex Adj	Multivariate Model §
Total Population	371/5642	ref.	ref.	390/4989	1.17 (1.02-1.35)	1.16 (1.00-1.33)	438/5272	1.25 (1.09-1.43)	1.19 (1.04-1.37)	474/5018	1.45 (1.26-1.66)	1.39 (1.22-1.60)
Age, y												
18-64	62/3146	ref.	ref.	47/2704	0.85 (0.58-1.24)	0.85 (0.58-1.24)	73/2818	1.26 (0.90-1.77)	1.25 (0.89-1.76)	81/2561	1.54 (1.10-2.14)	1.53 (1.09-2.14)
≥65	309/2496	ref.	ref.	343/2285	1.23 (1.05-1.43)	1.20 (1.03-1.40)	365/2454	1.23 (1.06-1.43)	1.17 (1.00-1.37)	393/2457	1.46 (1.25-1.69)	1.39 (1.20-1.62)
P for Trend					0.16	0.15		0.16	0.15		0.16	0.15
Sex												
Women	170/3123	ref.	ref.	169/2596	1.13 (0.91-1.39)	1.12 (0.90-1.39)	215/2700	1.41 (1.15-1.72)	1.33 (1.09-1.64)	214/2269	1.56 (1.27-1.90)	1.51 (1.23-1.85)
Men	201/2519	ref.	ref.	221/2393	1.20 (0.99-1.46)	1.18 (0.97-1.43)	223/2572	1.12 (0.93-1.36)	1.07 (0.88-1.30)	260/2749	1.36 (1.13-1.64)	1.30 (1.08-1.56)
P for Interaction					0.16	0.18		0.16	0.18		0.16	0.18
Race †												
White	311/4405	ref.	ref.	333/3848	1.17 (1.00-1.36)	1.16 (0.99-1.35)	383/4072	1.29 (1.11-1.50)	1.23 (1.06-1.44)	414/3876	1.48 (1.28-1.71)	1.41 (1.22-1.64)
Non-white	27/208	ref.	ref.	27/141	1.42 (0.83-2.43)	1.46 (0.84-2.53)	32/179	1.36 (0.81-2.27)	1.43 (0.85-2.42)	30/172	1.61 (0.96-2.72)	1.77 (1.04-3.01)
P for Interaction					0.93	0.98		0.93	0.98		0.93	0.98
Previous CVD												
None ‡	267/5089	ref.	ref.	288/4449	1.20 (1.02-1.42)	1.17 (0.99-1.39)	324/4670	1.32 (1.12-1.55)	1.26 (1.07-1.49)	362/4394	1.57 (1.34-1.84)	1.52 (1.29-1.78)
Yes	104/553	ref.	ref.	102/540	1.06 (0.80-1.39)	1.07 (0.81-1.41)	114/602	1.01 (0.77-1.32)	1.01 (0.77-1.32)	112/624	1.05 (0.81-1.38)	1.05 (0.80-1.37)
P for Interaction					0.068	0.084		0.068	0.084		0.068	0.084
Thyroxine use at BL												
None	371/5655	ref.	ref.	414/5122	1.16 (1.01-1.34)	1.15 (1.00-1.32)	431/5335	1.28 (1.11-1.47)	1.22 (1.06-1.41)	457/4809	1.43 (1.25-1.64)	1.38 (1.20-1.59)
Yes ||	9/69	ref.	ref.	13/78	1.69 (0.70-4-05)	1.66 (0.69-3.98)	16/120	1.59 (0.68-3.70)	1.68 (0.72-3.95)	30/275	1.41 (0.65-3.08)	1.48 (0.67-3.26)
P for Interaction					0.53	0.58		0.53	0.58		0.53	0.58

Abbreviations: Adj, adjusted; AF, atrial fibrillation; BL, baseline; CI, confidence interval; CVD, cardiovascular disease; E, events; HR, hazard ratio; NA, data not applicable; P, participants; ref., reference; TSH, thyroid-stimulating hormone

* This analysis was restricted to normal thyroid function, i.e. TSH and thyroxine in the reference range. From the overall sample a total of 9164 participants were excluded for this analysis with either missing measurements of fT4 or thyroid function outside the reference range. 479 participants of the Cardiovascular Health Study, 59 of the Osteoporotic Fractures in Men Study, 32 of the Bari Study, 137 of the Leiden 85+ Study, 125 of the Study of Health in Pomerania, 42 of the InChianti Study, 365 of the Rotterdam Study, 897 of the EPIC-Norfolk Study, and 57 of the Busselton Health Study. In participants of the Health ABC Study, fT4 was measured only in TSH $\geq$ 7.0 mIU/L; therefore all 2346 participants were excluded for this analysis. In the PROSPER Study, fT4 was measured only in participants with TSH <0.45mIU/l or TSH $\geq$4.5mIU/l; therefore, 4625 participants were excluded from this analysis.

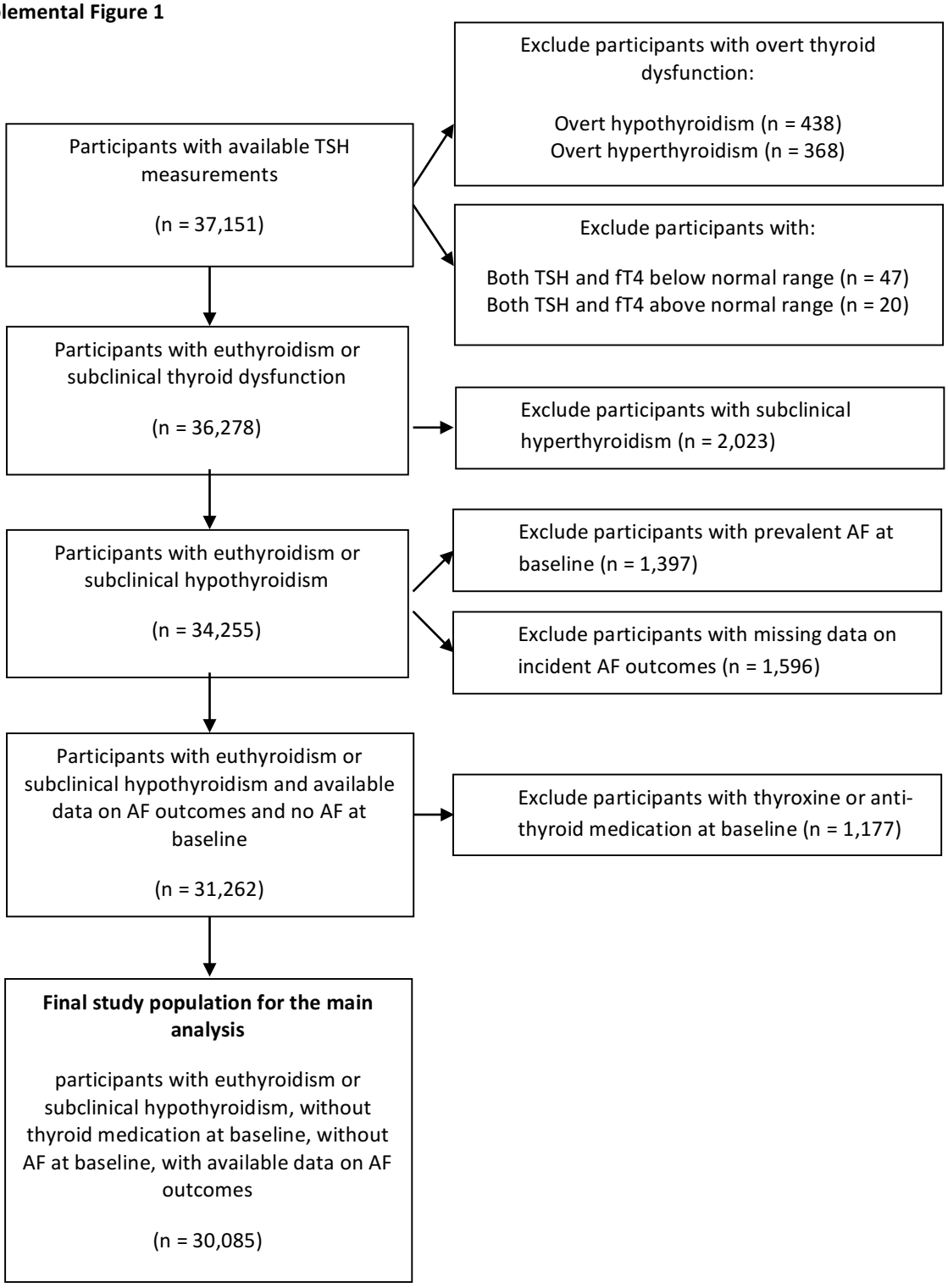
† African Americans, Hispanics, Asian, and others were considered as non-white population. Data on race were missing for all participants of the SHIP study, the InChianti Study, and the PROSPER Study, 51 participants of the Rotterdam Study and 37 of the EPIC-Norfolk Study.

‡ Previous cardiovascular was defined as a history of stroke, transient ischemic attack, myocardial infarction, angina pectoris, coronary angioplasty, bypass surgery. Participants without any of these events were considered having no previous cardiovascular disease.

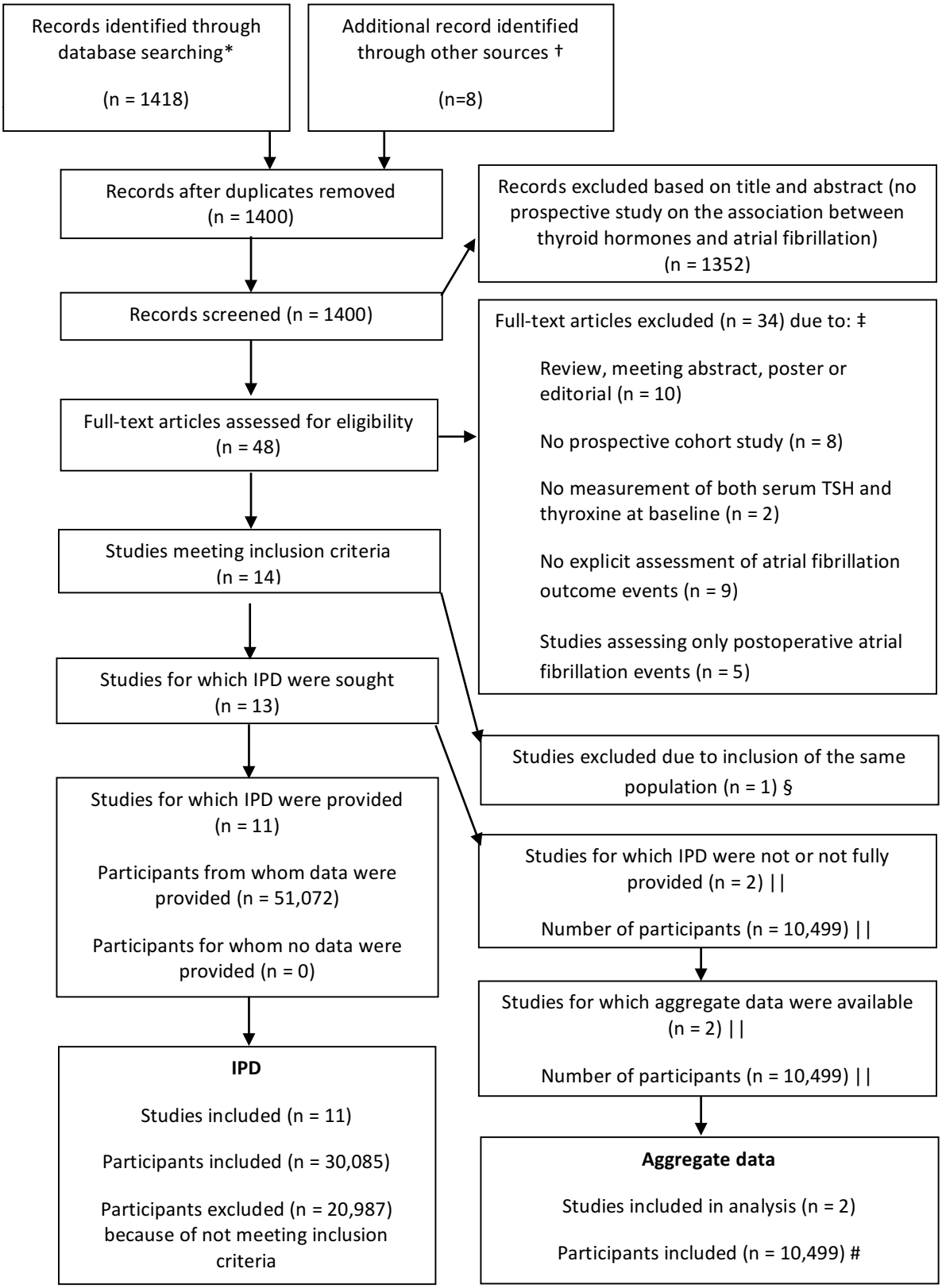
§ Adjusted for age, sex, systolic blood pressure, current and former smoking, diabetes, total cholesterol and prevalent cardiovascular disease.

|| 542 participants with available measurement of fT4 and normal thyroid function were on thyroxine at baseline: 167 participants of the CHS, 33 of the MrO2, 6 of the Bari, 5 of the Leiden 85+ Study, 76 of SHIP, 11 of the InChianti Study, 9 of the Rotterdam Study, 8 of the PROSPER Study, 224 of the EPIC-Norfolk Study, and 3 of the Busselton Health Study.

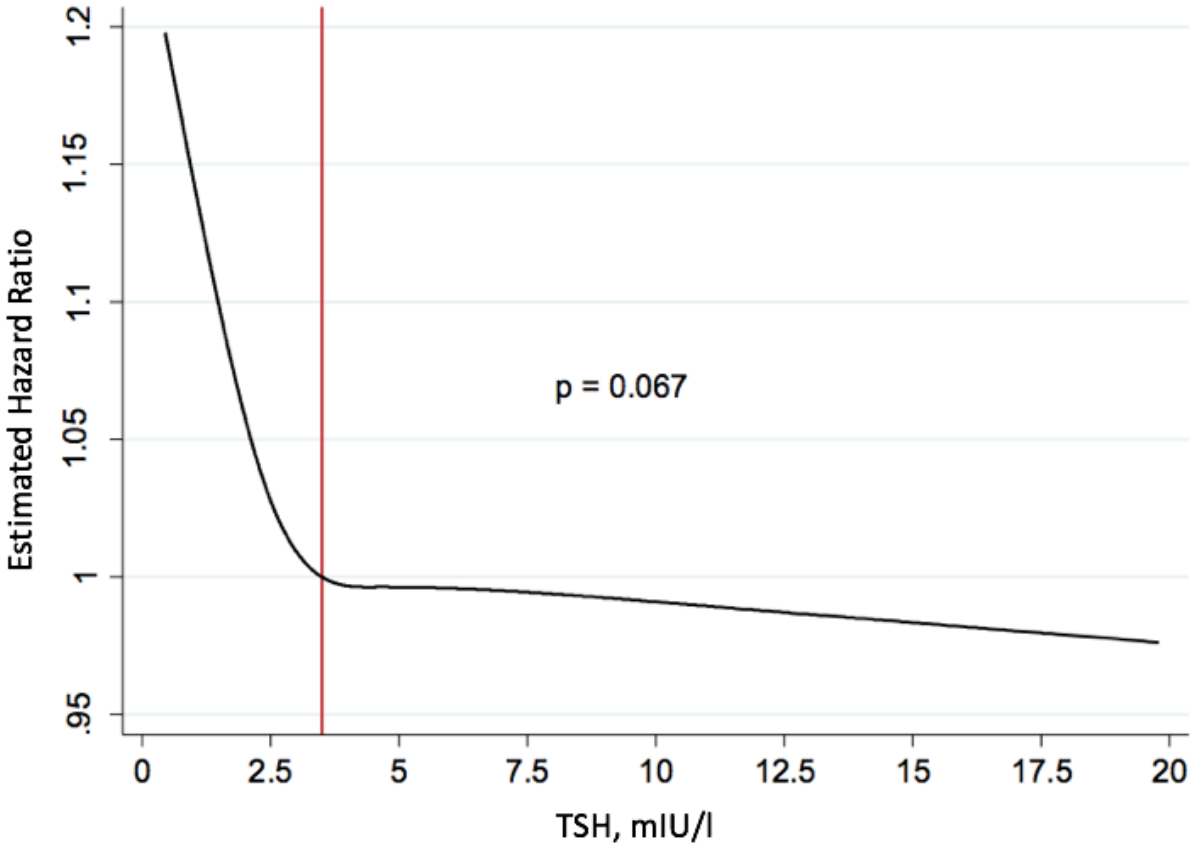
Supplemental Figure 1



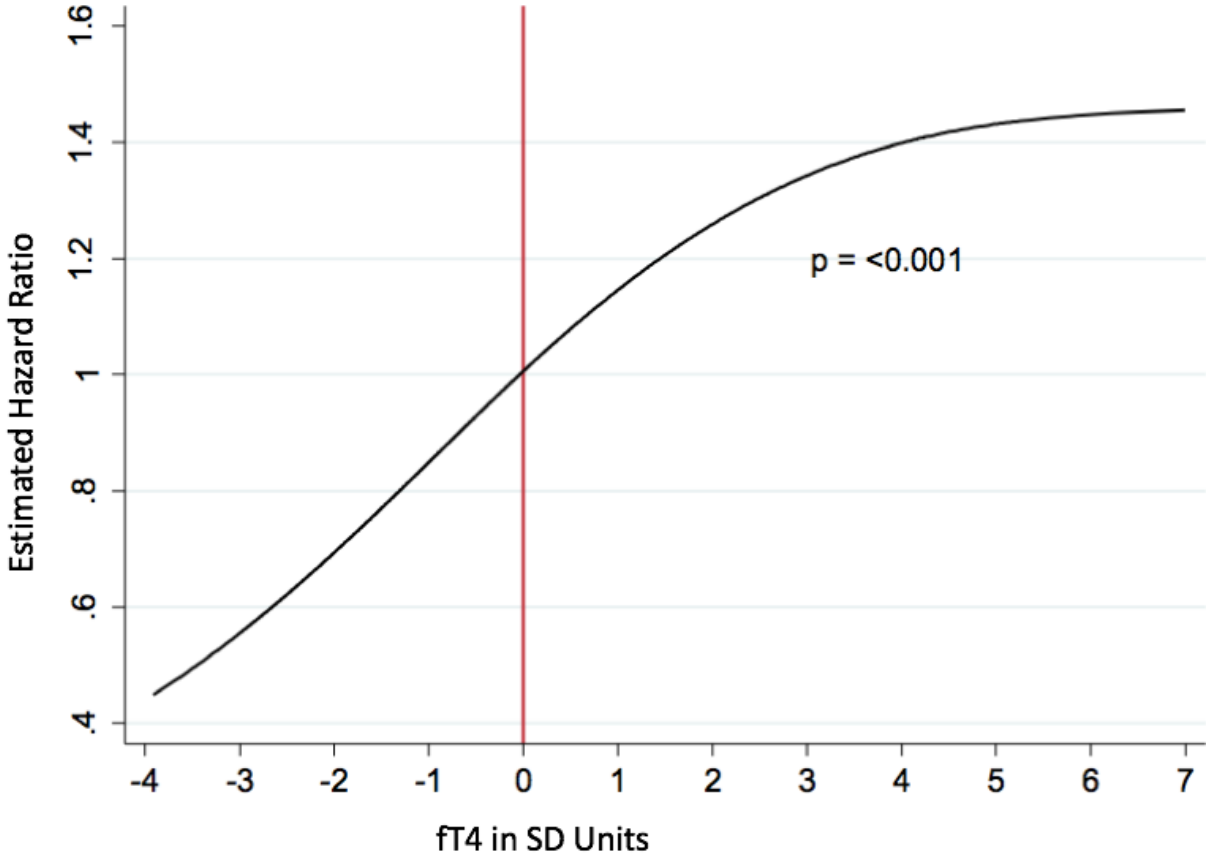
Supplemental Figure 2



Supplemental Figure 3.



Supplemental Figure 4.



Supplemental Figure 5.

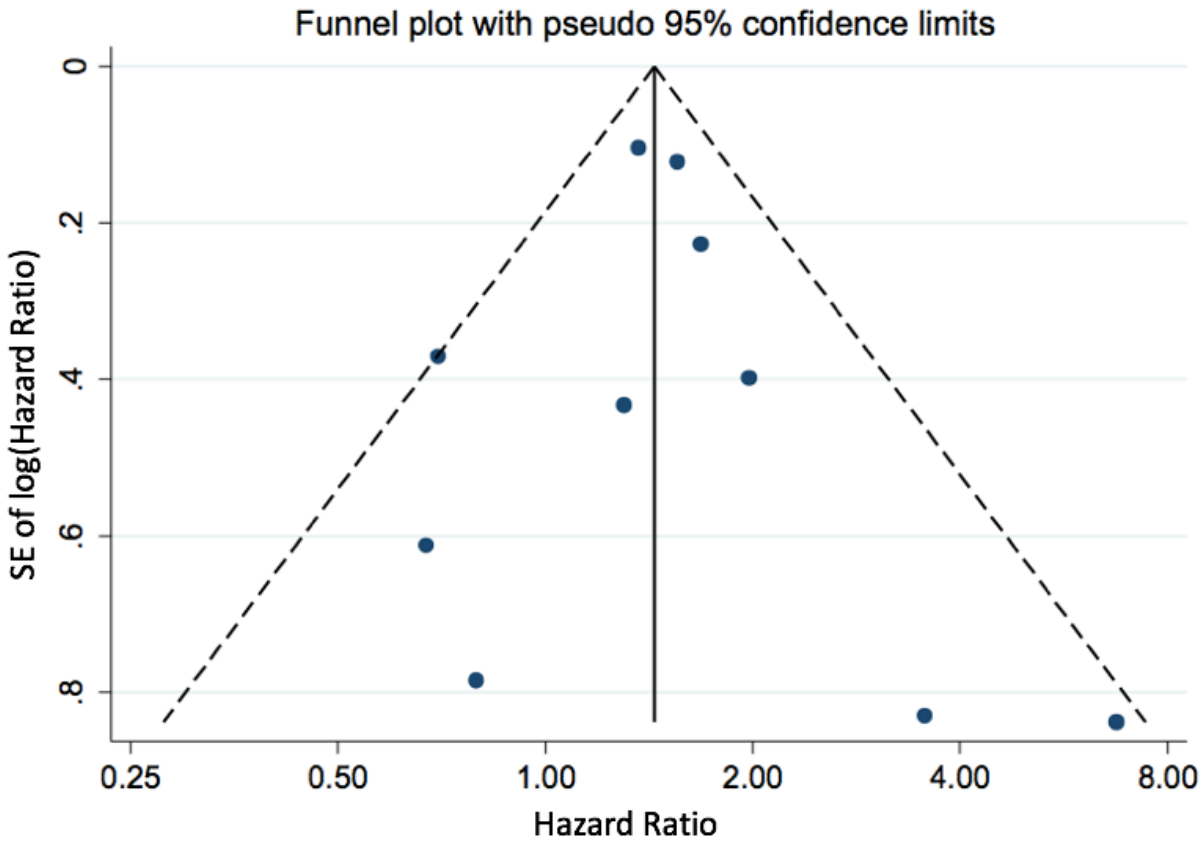


Figure Legends

Supplemental Figure 1. Selection of the final study population for the individual participant data analysis.

Abbreviations: AF, atrial fibrillation; fT4, free thyroxine; TSH, thyroid stimulating hormone.

Supplemental Figure 2. Study flow diagram**.** Studies evaluated for inclusion in the IPD analysis, adapted from PRISMA-IPD Statement Flow Diagram.[3] Abbreviations: IPD, individual participant data

* Until July 27, 2016

† from prospective cohorts participating in the international Thyroid Studies Collaboration that had prospective data on atrial fibrillation outcomes

‡ List of excluded full text articles in Supplemental Table 2

§Two articles retrieved through database searching included the same population of the Cardiovascular Health Study [4,5]

|| Data on 1759 euthyroid and subclinically hypothyroid participants from the Framingham Heart Study [6] were not provided free of charge. Among the 8740 participants included in the Rotterdam Study,[7] data of the 1426 participants included in the Rotterdam Study Cohort I that had been previously published [8] were provided, whereas data on 7314 participants of the Rotterdam Study Cohorts II and III were not provided.

Chaker and colleagues reported aggregate data of the Rotterdam Study Cohorts I, II, and III, therefore the individual participant data of Rotterdam Cohort I (that were included in our main analysis) were excluded for the sensitivity analysis including the aggregate data.[7]

Supplemental Figure 3. Restricted cubic spline plot for the association between continuous concentrations of thyroid stimulating hormone and atrial fibrillation. The p-value for a non-linear trend was 0.067. Abbreviations: TSH, thyroid stimulating hormone.

Supplemental Figure 4. Restricted cubic spline plot for the association between continuous concentrations of free thyroxine within the reference range and atrial fibrillation. The p-value for a non-linear trend was $\leq$0.001. Abbreviations: fT4, free thyroxine; SD, standard deviation.

Supplemental Figure 5. Funnel plot for the association between free thyroxine within the reference range and atrial fibrillation. Estimates of the highest fT4 quartile compared to the lowest fT4 quartile were considered. Abbreviations: fT4, free thyroxine; SE, standard error.

Supplemental References

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